REMARKS

Claims 1-3, 6, 7, 10-12, 15-21, and 41 are pending in the application and under active consideration. Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. § 102 (b).

35 U.S.C. § 103

Claims 1-3, 6, 7, 10-12, 15-19, and 41 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski et al. (Cellular Immunol. (1995) 160:224-231; hereinafter "Gorczynski") in view of Nakai et al. (Blood (1998) 91:4600-4607; hereinafter "Nakai"), and further in view of Wakita et al. (J. Biol. Chem. (1998) 273:9001-9006; hereinafter "Wakita").

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 and the Office's purported facts underlying the rejection on the following grounds.

The present claims are directed a method for preparing a non-human animal for screening for agents that modulate tolerance to a hepatitis C virus (HCV) immunogen and an animal prepared by the method. The method comprises exogenously delivering a nucleic acid encoding the immunogen to the liver of said animal by portal vein injection, under conditions that result in the sustained expression of the HCV immunogen in the liver thereby inducing immunological tolerance to said HCV immunogen, wherein the HCV immunogen is **expressed for at least one month** in said animal.

Gorczynski, the primary reference cited in the Office Action, does not teach or suggest the invention as claimed. Furthermore, there is no motivation provided by the Examiner to combine Gorzynski with the cited secondary references, Nakai and Wakita, to arrive at the claimed invention. In addition, even assuming, arguendo, that such motivation were present, the invention as claimed is not described in the cited combination of references, since the combination does not disclose an animal model for tolerance (1) to an infectious disease (specifically an HCV immunogen) that (2) is operative for at least one month.

Gorczynski was cited for teaching the "general concept that animals that are imunologically tolerant to an immunogen can be made by producing the sustained presence of a tolerance inducing immunogen in the liver of an animal." (Office Action of October 18, 2005 at

page 4). The Examiner further cites Gorczynski as teaching a method of making a mouse that is tolerant to skin allografts by infecting cells (an immunogen) into the portal vein of the mouse.

Gorczynski, however, is directed to the injection of spleen cells, something very different and distinct from an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed. Also, Gorczynski demonstrates tolerance to skin allografts but suggests nothing with respect to tolerance to an antigen from an organism that causes an infectious disease, specifically an HCV immunogen as claimed. Gorzynski also does not teach expression of an immunogen for at least one month; as also recited in the claims.

The present claims recite an animal having (1) sustained expression for one month, of (2) an HCV immunogen wherein (3) the animal is tolerant to the HCV immunogen. As detailed above, Gorzynski does not teach sustained expression for one month, tolerance for one month, or tolerance to an HCV immunogen. In fact, Gorzynski discloses a model for allograft tolerance, and does not give any direction or guidance on how to induce tolerance to <u>any</u> infectious agent.

The secondary reference of Nakai fails to cure the deficiencies of the primary reference Gorczynski. Nakai describes transduction of murine hepatocytes with recombinant adeno-associated virus vectors expressing human factor IX for the purpose of developing methods of gene therapy for hemophilia B. Nakai was cited by the Examiner as teaching the <u>sustained expression</u> of a gene in the liver of an animal using an adeno-associated viral particle that is delivered to the liver by portal vein injection.

Nakai does not disclose anything about HCV and fails to teach or suggest any method for inducing tolerance to an antigen in an animal model as claimed. In addition, the human factor IX expressed is not in any way related to an antigen or immunogen from an infectious agent, specifically an HCV immunogen as claimed.

The secondary reference of Wakita also fails to cure the deficiencies of the primary reference Gorczynski, either alone or in combination with Nakai. Wakita teaches Cre/loxP-mediated conditional expression of HCV proteins in the liver of transgenic mice. Wakita in fact teaches away from the claimed invention, in that the Cre/loxP system is used to control expression of HCV transgenes such than antigens are produced only transiently, as opposed to sustained expression for at least one month as claimed. Furthermore, as opposed to generating a

"tolerant" animal model, Wakita clearly states that at a minimum, an antibody response was produced in response to the transient expression of HCV antigens.(see page 9006, col. 1).

Wakita was cited by the Examiner as disclosing that sustained expression of HCV antigens in the liver can produce tolerance to the antigens:

> Furthermore, the prior art also recognizes that sustained expression of specific HCV genes in the liver of an animal can produce immunological tolerance to the HCV genes...[citing Wakita et al. 1998...] (Office Action of October 18, 2005 at page 4-5).

The Examiner goes on to assert that Wakita provides "a powerful tool to investigate the immune responses and pathogenesis of HCV infection."

Applicants respectfully submit that: (1) there is no sustained expression of any antigen demonstrated in Wakita; (2) Wakita does not disclose an animal that is tolerant to any antigen, especially an antigen from an infectious agent and especially an HCV immunogen, as claimed; The "powerful tool" allegedly disclosed by Wakita does not teach or suggest an HCV-tolerant animal that can be used for screening purposes, especially for screening for the immunomodulation of an antigen or immunogen from an infectious agent, especially an HCV immunogen and especially expression of the immunogen for at least one month.

Based in part on the above observations, the Examiner has asserted that:

> ...it would have been prima facie obvious to one of ordinary skill in the art at the time of filing that an animal having tolerance to an HCV gene...can be made by delivering the adeno-associated viral particle that has been modified to express HCV E1 or HCV E2 to the liver of the animal by portal injection, with a reasonable expectation of success." (Office Action of October 18, 2005 at page 3).

As motivation for combining the references, the Examiner repeats Wakita's teaching that an animal having sustained expression of HCV E1 or HCV E2 in the liver of a transgenic mouse results in an animal that can be used as a powerful tool to investigate the immune responses and pathogenesis of HCV infection and that it would have been recognized that portal injection of a vector that expresses a protein is an easier way of producing the animal that expresses a foreign gene than making a transgenic animal, as was done by Wakita.

As noted above, Gorczinski does not teach or suggest delivering a protein that is encoded by a nucleic acid. The Examiner has cited Gorczynski for teaching the general concept that animals that are tolerant to an immunogen can be made by producing the sustained presence of a

tolerance inducing immunogen in the liver of the animal. As support for this conclusion, the Examiner cites the teaching in Gorczynski that a mouse was made "...tolerant to skin allografts by injecting cells (i.e., an immunogen) into the portal vein of the mouse..." (Office Action of October 18, 2005 at page 4)

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

Applicants submit that the cited references do not disclose or suggest all the limitations of the present invention, especially since none of the references suggests sustained expression for at least one month of an antigen from an infectious agent, in particular an HCV immunogen. Thus, since the references together do not include all of the recited claim elements, a primae facie case of obviousness has not been established.

Even assuming, arguendo, that the cited references did together disclose all of the claim limitations, the Examiner has not provided any evidence indicating a motivation (either in the references or from the level of ordinary skill in the art at the time of filing) which would have provided reasonable expectation of success in combining the references to arrive at the claimed invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge.

Thus, even assuming that the references together encompass all of the claim limitations, there has not been a demonstration of an expectation of success in combining the elements. Gorzynski, the primary reference, is directed to generating tolerance to a tissue graft. One of the secondary references, Nakai, is directed to a method of treating hemophilia B via genetic therapy. The other secondary reference, Wakita, is directed to the efficient conditional expression of HCV genes in order to study the immune response or pathology of HCV gene products. Gorzynski does not teach or suggest (1) sustained expression of (2) an HCV immunogen for (3) at least one month. Nakai also does not teach or suggest sustained expression of an HCV immunogen for at least one month. Wakita also does not teach or suggest sustained expression of an HCV immunogen for at least one month. Thus, contrary to the

Examiner's assertions, none of the cited references teach or suggest two essential limitations of the claims: (1) sustained expression for at least one month of (2) an HCV immunogen.

No motivation to combine the three references has been provided. Withdrawal of this rejection is respectfully requested.

Claims 1-3, 6, 7, 10-12, 15-21, and 41 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over the reference of Gorczynski in view of Nakai et al. (*supra*), further in view of Wakita et al. (*supra*), and further in view of Donnelly et al. (WO 97/47358). The Final Office Action further alleges that "[o]ne or ordinary skill in the art would have been motivated to combine the teachings and make the HCV NS5 tolerant animal based on the teaching of Wakita..."

There is nothing in the secondary reference of Donnelly to cure the deficiencies of Gorczynski, Nakai, and Wakita. Donnelly is silent on the expression of antigens to induce immunological tolerance to HCV antigens and is instead directed to expression of HCV antigens. The focus of Donnelly is on therapeutic and prophylactic vaccines capable of eliciting an immune response against HCV. Donnelly describes <u>intramuscular</u> injection of polynucleotides encoding HCV antigens to generate antibody and CTL immune responses against HCV. See, *e.g.*, page 5, lines 25-27 and page 11, lines 29-33. Donnelly fails to teach or suggest anything regarding nucleic acid immunization by injection in the portal vein, or sustained expression of antigens in the liver to achieve immunological tolerance.

In direct contrast to the claimed invention, Donnelly teaches eliciting an immune response to an HCV antigen, while the present claims are directed to the induction of tolerance (i.e., lack of an immune response (See page 5 of the application as filed, where tolerance is defined as the state where "...effector cells of the immune system do not respond to an immunogen"). Thus, Donnelly teaches away from the claimed invention, which requires suppression of the immune response.

Based on the foregoing, it is respectfully submitted that the combined references do <u>not</u> encompass all of the claimed limitations, since none of the references teach or suggest sustained expression of an HCV immunogen for at least one month to induce tolerance to the immunogen. Furthermore, even assuming arguendo that the combination of references did teach or suggest all

of the claimed limitations, the Examiner has failed to identify the motivation for combining the references.

For at least these reasons, withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested. If the rejection is maintained, applicant requests clarification regarding the Examiner's position, either in the form of scientific literature, or by a declaration pursuant to 37 CFR §1.104(d)(2).

CONCLUSION

In light of the above remarks, Applicant submits that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicant invites the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

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